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Supplementary appendix

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Air Pollution and Coronary Artery Calcification: Supplementary Appendix

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Number & Timing of Measurements

Figure S1. Number of measurements included in analyses of CAC progression. The numbers in green boxes (second to last row) represent the number of measurements included in the analysis of outdoor $PM_{2.5}$. The numbers in blue boxes (last row) represent the number of measurements included in the analysis of individually-weighted, ambient-derived $PM_{2.5}$ exposure ($PM_{2.5iwa}$)

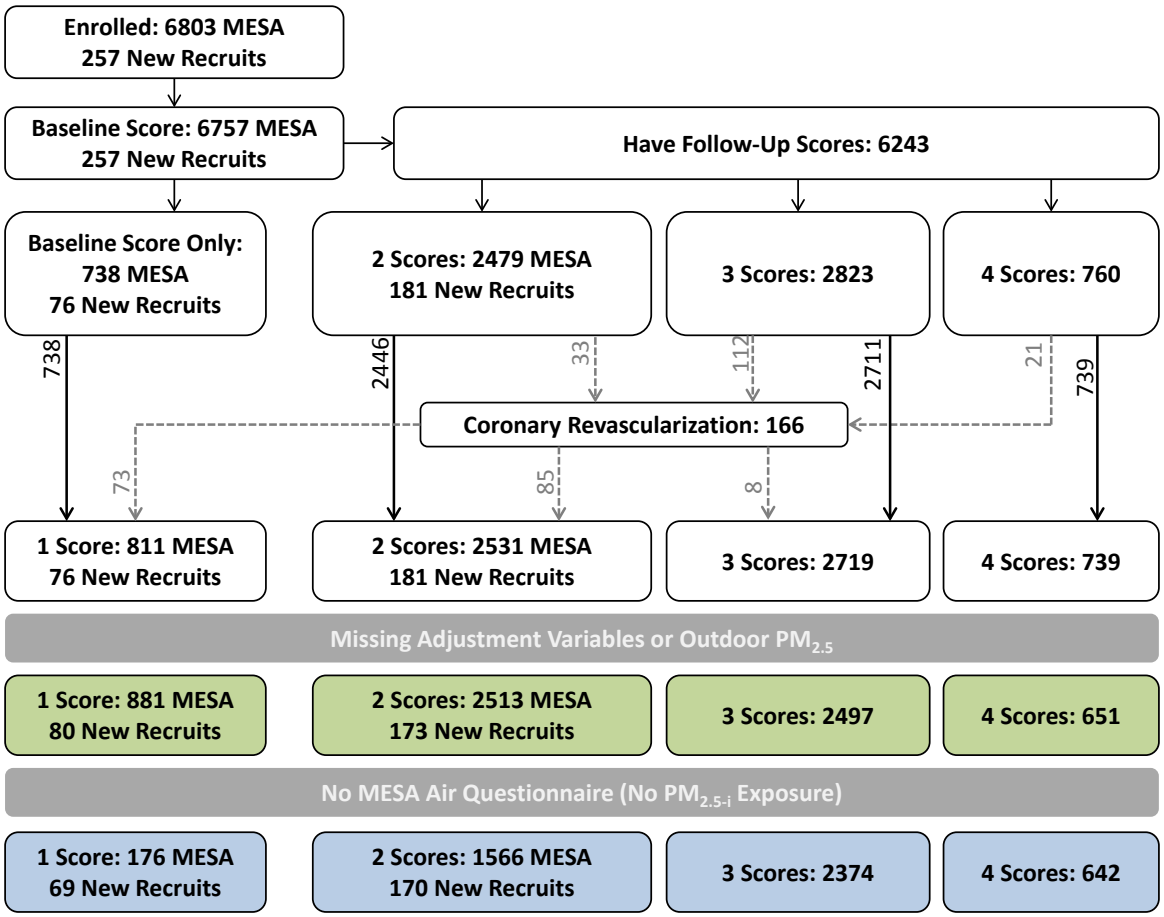
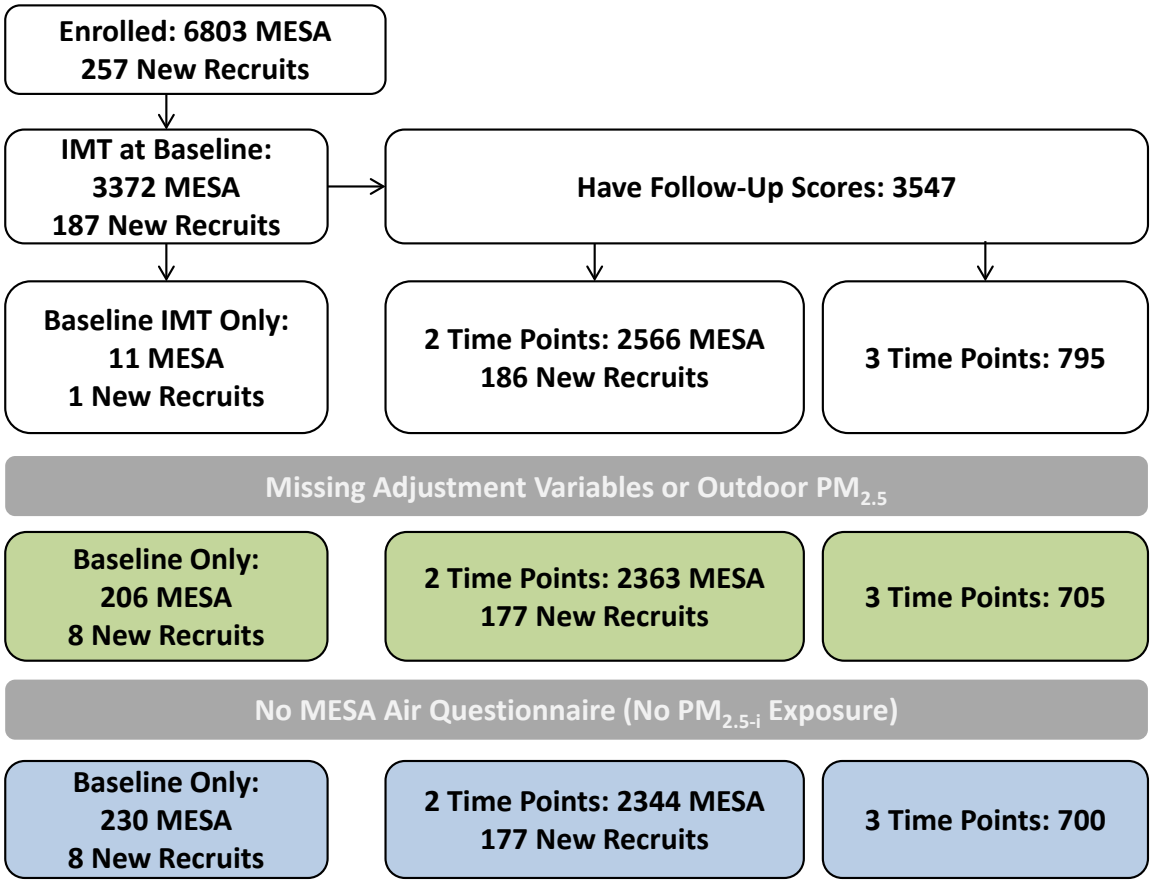


Figure S2. Number of measurements included in analyses of IMT progression. The numbers in green boxes (second to last row) represent the number of measurements included in the analysis of outdoor $PM_{2.5}$. The numbers in blue boxes (last row) represent the number of measurements included in the analysis of individually-weighted, ambient-derived $PM_{2.5}$ exposure ($PM_{2.5iwa}$)



Health Model Details

Analysis of change in measures of subclinical disease processes is challenging. The extent of disease at baseline can be considered to be likely associated with progression of disease both due to the exposure of interest, measured confounders and unmeasured confounding factors. There is a desire to understand the relationship between the exposure of interest and the progression of disease adjusting for all potential confounders (measured and unmeasured) and to avoid bias in the analysis. The mixed effects model we used in this analysis jointly models the cross-sectional and longitudinal relationships between air pollution exposure and the outcomes. The cross-sectional terms model an estimated baseline and control for that baseline. The cross-sectional relationships between air pollution and other risk factors with the outcomes can produce biased results in a progression analysis that controls for measured baseline.[1,2] Any measurement error exacerbates this bias.[1,2] Adjusting for an estimated baseline allowed us to control for cross-sectional confounding without inducing bias.

The mixed model provides two additional benefits: 1) individuals with a variable number of observations and varying lengths of follow-up, or even a single observation, can be included in the analysis and 2) the assumption that data is missing completely at random (MCAR) is not required. Therefore, selection bias is of less concern using this method compared to methods which require full follow-up for all participants or the MCAR assumption, such as generalized estimating equations (GEE) or repeated measures analysis of variance (ANOVA).

The specific form of the model is as follows, subjects indexed by *i* and exams indexed by *v*:

$$Y_{iv} = [\alpha_0 + X_{i0}\alpha_1 + a_i] + [t_{iv}\beta_0 + W_{iv}t_{iv}\beta_1 + t_{iv}b_i] + [U_{iv}\gamma_1 + \epsilon_{iv}]$$

where

Y_{iv} = Outcome measurement for subject *i* at v^{th} follow-up exam

X_{i0} = time-invariant cross-sectional confounders and risk factors at Exam 1 for subject *i*, including mean air pollution exposure during the year 2000 (used as a proxy for chronic exposure prior to enrollment in MESA Air). Also includes site indicator and, for IMT, an indicator for right or left common carotid.

W_{iv} = possibly time-varying longitudinal confounders and risk factors at exam *v* for subject *i*, including mean air pollution exposure during the time period between baseline (v = 0) and v^{th} follow-up exam, rounded to the nearest whole year

U_{iv} = time-varying variables to adjust measurements at exam *v* for subject *i*, primarily CT scanner in the CAC analyses

t_{iv} = time in years from baseline (v = 0) to the v^{th} follow-up exam for subject i

β_0 = Outcome progression (annual rate of change) in average participants in the reference group

β_1 = coefficients for interaction between risk factors and time; this includes the air pollution by time interaction which is interpreted as a rate (association between air pollution and annual progression)

α_0 = average CAC measurement at Exam 1 for participants in the reference group

α_1 = coefficients for cross-sectional associations between baseline outcome measurements and risk factors (including year 2000 air pollution exposure)

γ_1 = coefficients for cross-sectional associations between time-varying variables and CAC measurements at all exams

a_i = subject-specific random intercept, which is nested within a neighborhood-specific intercept

b_i = subject-specific random slope

ε_{iv} = error associated with Y_{iv}

The model is comprised of three parts, separated above by square brackets. They are: 1) the cross-sectional relationship between the baseline outcome and values of covariates at baseline, 2) the longitudinal relationship to model rate of change, and 3) time-varying "transient" terms that adjust for variables relevant to specific measurements. The cross-sectional terms in the model are equivalent in interpretation to terms from a cross-sectional model of the outcome at baseline. These fixed effects (α_1), together with the random intercepts (a_i), model subject-specific intercepts. The longitudinal terms model an overall progression rate (β_0), interpreted as the rate of change in outcome for a subject with no additional risk factors (i.e. all terms W_i=0), and incorporate terms which adjust that rate (β_1) according to the association between progression rate and risk factors. Values of covariates included in the transient part (U_{iv}) are time-varying but the transient adjustment does not modify the slope. The function of the transient terms is to adjust follow-up measurements that were measured under different conditions from the original. Removing systematic differences due to different conditions allows the slope to be estimated based on the measurements as if they had been measured under the same conditions.

Air Pollution Model Details

Air pollution modeling was conducted using a custom-built R package, designed to estimate time-varying air pollution concentrations from irregular air pollution measurements.[3] Details of the statistical method have been published, as have the detailed predictive model used in this paper.[4,5]

Long-Term Averaging of Pollutant Exposures

Mean predictions between the baseline exam and each follow-up exam (i.e. "long term averages") were calculated. This was done by averaging the time- and location-specific two-week predictions, rounding the between-exam time period to the nearest whole year to account for seasonal and spatial clustering of recruitment and examinations.

Individually-Weighted, Ambient-Derived $PM_{2.5}$

One limitation of most epidemiological studies of air pollution in developed nations is that health effects are linked to outdoor pollutant concentrations, even though most residents of these countries spend the majority of

their time indoors. There are several reasons to believe that an analysis of outdoor concentrations is the most appropriate analysis. Public policy typically addresses outdoor air quality, with concentrations outdoors being subject to regulation. Highly accurate characterization of infiltration patterns over time and individual times spent outdoors are prohibitively expensive to assess and would involve substantial burden on study participants. MESA Air deployed a concerted effort to produce reasonable estimates of infiltration, incorporating local meteorology, home characteristics, and window-opening habits.[6] We endeavored to capture typical indoor-outdoor weighting using time-location questionnaires.[7]

Individually-weighted, ambient derived $PM_{2\cdot5}$ exposures ($PM_{2\cdot5iwa}$) were calculated as follows:

$$Y_i = \frac{1}{n}\sum_{k=1}^{n} X_k t_k + X_k(1-t_k)F_{inf:k}$$

Where:

Y_i: $PM_{2\cdot5\ iwa}$ for subject i

X_k: Outdoor $PM_{2\cdot5}$ concentration as predicted by the area-specific spatio-temporal model, for each of n 2-week periods during the exposure period of interest, indexed by k

t_k: Proportion of time spent outdoors during 2-week period k

$F_{inf:k}$: Predicted $PM_{2\cdot5}$ infiltration fraction for 2-week period k

Light absorption coefficient as a metric of black carbon

In the manuscript we have referred to increments black carbon (BC) in units of $\mu g/m^3$,although black carbon was assessed by light absorption coefficient (LAC). Co-located MESA Air measurements of LAC with air quality agency thermal optical measurements of elemental carbon at AQS sites provided a conversion of $0\cdot5x10^{-5}m^{-1}$ of light absorption to $0\cdot5\ \mu g/m^3$.[8]

Dose-Response Method

The concentration-response relationship between long-term exposure to $PM_{2\cdot5}$ and the rate of CAC progression was modeled using a thin plate regression spline with 5 degrees of freedom included as interaction terms with follow-up time. The final curve (main manuscript Figure 3) depicts the contribution of this spline as a

function of long-term exposure to $PM_{2.5}$. Both baseline and follow-up exposures were mean centered for this analysis. Baseline exposure entered the model as a linear term only.

Adjustment Variable Details

The questionnaires and physical examinations administered to MESA participants have been described previously.[9] Smoking status was categorized as: Never, no second-hand smoke (SHS) exposure; Never, any SHS exposure; Former, no SHS exposure; Former, SHS exposure; Current. Pack-years were also included as a continuous variable. Physical activity was included by indicators for quartile of intentional exercise minutes.[10] Employment outside the home was included as a binary indicator. Educational attainment was collapsed into the following four categories: < high school; high school; some college or technical school; bachelor's degree or more.[11] Diabetes was defined as fasting glucose >6·99 mmol/L (126 mg/dL) or use of hypoglycemic medication.[12] Instead of BMI or waist/hip ratio, we adjusted for the following measures of adiposity: weight, 1/height, 1/height^2, waist circumference, and 1/(hip circumference). Measured HDL, total cholesterol, triglycerides, fibrinogen, CRP, and creatinine were included as continuous variables. Statin use was included as binary and time-varying. Hypertensive medication was included as binary. Neighborhood SES index was included as a continuous variable.[13] Family history of premature CVD was defined as myocardial infarction/heart attack, stroke/brain attack, or cardiovascular procedure (coronary bypass or balloon angioplasty) in a female primary relative (parent, sibling, or child) under the age of 65 or a male primary relative under the age of 55 and was included as binary. Since most participants reported income at some but not all exams, a variable for "permanent income" was calculated as the mean across all available responses, using the midpoints of the categories:

Values used to average income across exams (USD).

Category Option	Value Used for Averaging
< $5,000	$2,500
$5,000-7,999	$6,500
$8,000-11,999	$10,000
$12,000-15,999	$14,000
$16,000-19,999	$18,000
$20,000-24,999	$22,500
$25,000-29,999	$27,500
$30,000-34,999	$32,500
$35,000-39,999	$37,500
$40,000-49,999	$45,000
$50,000-74,999	$62,500
$75,000-99,999	$87,500
$100,000 +	$125,000

Additional Sensitivity Analyses

Results from additional sensitivity analyses not reported in the main text are presented in Table S6. Analyses excluding participants with the highest overall progression, participants with renal failure (eGFR < 30), or those with calcium metabolism abnormalities (serum phosphate > 4·5 mg/dl) at baseline were all consistent with the primary analyses. Furthermore, results were unchanged by the exclusion of the neighborhood-specific random effects or participants with extremely high exposures. The association between nearest monitor $PM_{2·5}$ and CAC progression was attenuated compared to the association with modeled $PM_{2·5}$, as would be expected due to the exposure misclassification inherent in nearest monitor concentrations. Analyses that were not adjusted for city or scanner resulted in weaker associations.

Power Calculations

Several sets of power calculations supported the MESA Air study design. The parent study (MESA) targeted a sample size adequate to assess risk factors for mortality. The expected number of cardiac events was calculated based on prior results from the Atherosclerosis Risk in Communities (ARIC) study, Cardiovascular Health Study (CHS), National Longitudinal Mortality Study, and National Health Interview Study.[9] Power for the analysis of subclinical atherosclerosis progression, defined as progression of CAC and IMT, associated with air pollution, was evaluated in 2003 for the original MESA Air proposal. At that time, long-term $PM_{2·5}$ concentrations were simulated using a lognormal distribution with a geometric mean and standard deviation determined from EPA monitoring data. Simulated CAC outcomes were based on either early MESA data and IMT on existing clinical trials data.[14] Setting a goal of 3600 scans to be conducted during the final examination period (2010-2012), the study was designed to be adequately powered to detect air pollutant effects of 2 Agatston units/year or 7 μm/year IMT per 10 $\mu g/m^3$ $PM_{2·5}$. These power calculations were re-evaluated in 2008 at the time of the mid-course progress report and study continuation process. At that time, $PM_{2·5}$ exposures were estimated based on year 2006 measurements at long-term regulatory and study-specific monitoring sites. The calcium outcome was simulated based on the distribution of early MESA measurements, and the results indicated 80% power to detect a within-city effect of 0·0078 change in ln(CAC+25) per $\mu g/m^3$-year of $PM_{2·5}$. The IMT outcome was simulated based on pre-existing data,[15] and the results indicated 80% power to detect a within-city effect of 3·5 μm/year per $\mu g/m^3$.

Supplementary Tables

In this section, we report additional descriptive statistics and sensitivity analyses that may be of interest.

Tables S1 and S2 present further detail on the air pollution exposures that were used. Table S1 provides descriptive statistics for the $PM_{2\cdot5iwa}$ exposure, with statistics for the outdoor PM2·5 predictions for comparison. Table S2 presents the correlations between the exposures of interest, both overall and within-site.

In table S3, we provide demographic characteristics by time to last CT measurement that was included in our main analysis. Overall, participants with longer follow-up tended to be younger, have lower blood pressure, have more education, and were less likely to be diabetic.

In Table S4, we report the full results from staged models for all air pollution exposures, including $PM_{2\cdot5iwa}$. We found that while the association between individually-weighted, ambient-derived $PM_{2\cdot5}$ exposure and CAC progression was positive, the magnitude of this association was weak compared to the association between outdoor $PM_{2\cdot5}$ concentration and CAC progression.

Despite our efforts to produce individually-weighted exposure concentrations that take into account indoor concentrations and time in the indoor and outdoor space, we do not consider these predicted exposures to represent the best approach to use in epidemiological study. As these predictions represent the product of two different modifiers of outdoor concentration—each imperfectly assessed—we are concerned that they provide additional error to our exposure estimation. Full characterization of time-location patterns and indoor exposures is notoriously difficult, and the challenge of ascertaining highly resolved, individualized micro-environmental exposure estimates over years of follow-up remains unmet.

Tables S5 through S8 provide the results from additional analyses of air pollution exposures and CAC progression. Table S5 shows the associations observed in staged models between relative change in CAC score and single pollutants. In Table S6, results from the analysis of effect modification are reported for both outdoor $PM_{2\cdot5}$ and NO_X. Table S7 provides the results from the two-pollutant models. The attenuation of the effects and widened confidence intervals of $PM_{2\cdot5}$ and NO_X when jointly estimated are possibly attributable to the high within-city correlation of 0·87 between these pollutants (see Table S2). Table S8 presents effect modification analyses of the association between CAC and $PM_{2\cdot5}$ or NO_X.

IMT was considered an *a priori* outcome of MESA Air. Table S9 provides the descriptive statistics for the subgroup of the cohort that was included in the analyses of air pollution and IMT progression. Table S10 presents the full, staged results from these analyses. Overall, these analyses were consistently null.

Table S1. Mean and (standard deviation) for individually-weighted, ambient derived $PM_{2.5}$ exposures ($PM_{2.5iwa}$). The long-term average was calculated over the time rounded to the nearest whole year between baseline and last CAC measurement for each participant.

	Year 2000 $PM_{2.5iwa}$ ($\mu g/m^3$)	Long-Term $PM_{2.5iwa}$ ($\mu g/m^3$)
Winston-Salem	9·0 (1·4)	6·3 (2·8)
New York	11·7 (2·1)	9·2 (4·3)
Baltimore	9·8 (1·8)	6·8 (3·8)
St. Paul	7·7 (1·3)	5·3 (2·4)
Chicago	10·0 (1·7)	7·5 (3·2)
Los Angeles	16·5 (2·1)	11·1 (6·0)

Table S2. Air pollution exposure prediction correlations.

Year 2000, Overall					**Long-Term*, Overall**				
	$PM_{2.5}$	NO_X	NO_2	BC		$PM_{2.5}$	NO_X	NO_2	BC
NOx	0·66				NOx	0·78			
NO_2	0·64	0·93			NO_2	0·83	0·97		
BC	0·68	0·91	0·92		BC	0·82	0·92	0·93	
$PM_{2.5iwa}$	0·85	0·74	0·72	0·75	$PM_{2.5iwa}$	0·93	0·85	0·88	0·88
Year 2000, Within-Site†					**Long-Term*, Within-Site†**				
	$PM_{2.5}$	NO_X	NO_2	BC		$PM_{2.5}$	NO_X	NO_2	BC
NOx	0·54				NOx	0·87			
NO_2	0·63	0·74			NO_2	0·92	0·95		
BC	0·63	0·67	0·72		BC	0·89	0·90	0·93	
$PM_{2.5iwa}$	0·56	0·43	0·44	0·44	$PM_{2.5iwa}$	0·95	0·87	0·91	0·88

* Based on the long-term average over the time rounded to the nearest whole year between baseline and last CAC measurement for each participant

† Calculated after subtracting the city-specific mean from each observation

Table S3. Participant characteristics by follow-up duration. Most individuals' last CT scan occurred in Exam 2, 3, or 5.

Characteristic [units]	Whole Cohort	Baseline Only	Up to 7 Years' Follow-Up	More Than 7 Years' Follow-Up
Year 2000-2010 Average $PM_{2.5}$ [$\mu g/m^3$]	14·3 (2·5)	14·6 (2·7)	14·4 (2·5)	14·0 (2·3)
Number of Participants	6795	960	2954	2881
Follow-Up Time	5·3 (3·9)	--	2·9 (1·2)	9·6 (0·6)
Outcome				
Baseline [Agatston Units]	145 (407)	231 (571)	171 (440)	90 (278)
Progression [Agatston/year]	24 (57)	--	28 (69)	18 (36)
Demographics				
Age	62 (10)	64 (10)	63 (10)	60 (9)
Male	3202 (47%)	474 (49%)	1399 (47%)	1329 (46%)
Race/Ethnicity				
Caucasian	2678 (39%)	347 (36%)	1201 (41%)	1130 (39%)
Chinese	795 (12%)	116 (12%)	341 (12%)	338 (12%)
African-American	1824 (27%)	264 (28%)	776 (26%)	784 (27%)
Hispanic	1498 (22%)	233 (24%)	636 (22%)	629 (22%)
Education				
Less Than High School	1209 (18%)	241 (25%)	569 (19%)	399 (14%)
High School	1209 (18%)	169 (18%)	533 (18%)	507 (18%)
Some College/Technical	1951 (29%)	265 (28%)	822 (28%)	864 (30%)
College or Graduate	2426 (36%)	285 (30%)	1030 (35%)	1111 (39%)
Smoking Status				
Never	3253 (48%)	433 (45%)	1403 (47%)	1417 (49%)
Former	2565 (38%)	374 (39%)	1124 (38%)	1067 (37%)
Current	977 (14%)	153 (16%)	427 (14%)	397 (14%)
General Health Characteristics				
BMI [kg/m2]	28 (5)	28 (6)	28 (6)	28 (5)
Systolic Blood Pressure [mmHg]	126 (21)	131 (23)	127 (22)	124 (20)
HDL [mg/dl]	51 (15)	51 (16)	51 (15)	51 (15)
LDL [mg/dl]	117 (32)	117 (33)	117 (32)	118 (31)
Total Cholesterol [mg/dl]	194 (36)	194 (38)	194 (36)	195 (35)
Hypertension	3024 (45%)	494 (51%)	1352 (46%)	1178 (41%)
Statin Use	1041 (15%)	156 (16%)	449 (15%)	436 (15%)
Diabetes				
Normal	4969 (85%)	631 (66%)	2132 (72%)	2206 (77%)
IFG	955 (16%)	149 (16%)	418 (14%)	388 (13%)
Diabetic	866 (13%)	178 (19%)	402 (14%)	286 (10%)

Table S4. Results for the associations between air pollution exposures and CAC progression from staged models. Results are presented in Agatston units/year.

Model	$PM_{2.5}$ (5 $\mu g/m^3$)	NO_X (40 ppb)	NO_2 (10 ppb)	BC (0·5 $\mu g/m^3$)*	$PM_{2.5iwa}$ (5 $\mu g/m^3$)
1	4·0 (1·3, 6·6)	5·0 (1·2, 8·7)	2·8 (-0·1, 5·7)	0·6 (-3·2, 4·4)	1·2 (-1·7, 4·1)
2	4·4 (1·7, 7·1)	4·9 (1·1, 8·7)	2·9 (-0·1, 5·8)	-0·2 (-3·9, 3·6)	1·4 (-1·5, 4·3)
3	4·1 (1·4, 6·8)	4·8 (0·9, 8·7)	2·7 (-0·3, 5·7)	0·1 (-3·8, 4·1)	1·3 (-1·7, 4·3)
4	4·1 (1·3, 6·8)	4·6 (0·7, 8·5)	2·3 (-0·7, 5·3)	0·6 (-3·3, 4·5)	0·2 (-2·9, 3·3)
5	4·3 (1·6, 7·0)	4·9 (1·0, 8·9)	2·7 (-0·3, 5·7)	0·3 (-3·6, 4·3)	1·0 (-2·0, 4·0)

* Black carbon (BC) as measured by light absorption coefficient, where $0{\cdot}5x10^{-5} m^{-1} \approx 0{\cdot}5\ \mu g/m^3$

Model 1 includes age, sex, race/ethnicity, site, and scanner type

Model 2 = Model 1 + employment outside the home, smoking status, second-hand smoke exposure, physical activity, adiposity, cholesterol, statin use

Model 3 (main model) = Model 2 + neighborhood SES index, income, education

Model 4 = Model 3 + hypertension, systolic and diastolic blood pressure, anti-hypertensive medication, diabetes

Model 5 = Model 4 + family history of premature CVD, fibrinogen, c-reactive protein, creatinine

Table S5. Association between air pollutant exposures and relative change in CAC progression, results from staged models. Results are exponentiated coefficients from ln(Agatston + 25).

Model	$PM_{2·5}$ (5 µg/m^3)	NO_X (40 ppb)	NO_2 (10 ppb)	BC (0·5 µg/m^3)*	$PM_{2·5iwa}$ (5 µg/m^3)
1	1·016 (1·010, 1·023)	1·014 (1·006, 1·023)	1·009 (1·003, 1·016)	1·005 (-1·002, 1·012)	1·010 (1·003, 1·017)
2	1·017 (1·010, 1·024)	1·013 (1·005, 1·022)	1·009 (1·002, 1·015)	1·002 (-1·005, 1·010)	1·010 (1·004, 1·017)
3	1·016 (1·009, 1·023)	1·011 (1·002, 1·019)	1·007 (1·000, 1·013)	1·000 (-1·007, 1·008)	1·008 (1·001, 1·015)
4	1·017 (1·010, 1·024)	1·010 (1·002, 1·019)	1·007 (1·000, 1·013)	1·001 (-1·006, 1·008)	1·009 (1·002, 1·017)
5	1·016 (1·009, 1·023)	1·011 (1·002, 1·020)	1·006 (1·000, 1·013)	1·000 (-1·008, 1·008)	1·008 (1·001, 1·015)

* Black carbon (BC) as measured by light absorption coefficient, where $0·5x10^{-5}m^{-1} \approx 0·5$ µg/m^3
Model 1 includes age, sex, race/ethnicity, site, and scanner type
Model 2 = Model 1 + employment outside the home, smoking status, second-hand smoke exposure, physical activity, adiposity, cholesterol, statin use
Model 3 (main model) = Model 2 + neighborhood SES index, income, education
Model 4 = Model 3 + hypertension, systolic and diastolic blood pressure, anti-hypertensive medication, diabetes
Model 5 = Model 4 + family history of premature CVD, fibrinogen, c-reactive protein, creatinine

Table S6. Additional selected sensitivity analyses. Results are presented in Agatston units/year.

Model	$PM_{2·5}$ (5 µg/m^3)	NO_X (40 ppb)	NO_2 (10 ppb)
Nearest monitor	2·9 (-0·1, 6·8)	--	--
Excluding eGFR > 30 at baseline	4·2 (1·5, 6·9)	4·9 (0·9, 8·8)	2·6 (-0·3, 5·6)
Excluding phosphate > 4·5 mg/dL at baseline	3·8 (1·0, 6·6)	3·9 (-0·1, 7·9)	3·0 (-0·1, 6·1)
Excluding 146 participants with raw progression rate > 250 Agatston units/year	4·0 (1·9, 6·2)	3·5 (0·4, 6·5)	2·7 (0·4, 5·0)

Each model also included age, sex, race/ethnicity, site, scanner type, employment outside the home, smoking status, second-hand smoke exposure, physical activity, adiposity, cholesterol, statin use, neighborhood SES index, income, and education.

Table S7. Results from CAC analyses including two air pollution exposures. The primary result for each air pollution exposure (i.e. the result from the single exposure model) is presented in the top row, for comparison with the results below as adjusted for co-pollutants. Results are presented in Agatston units/year.

Co-Pollutant	$PM_{2·5}$ (5 µg/m^3)	NO_X (40 ppb)	NO_2 (10 ppb)	BC (0·5 µg/m^3)*	$PM_{2·5-i}$ (5 µg/m^3)
Primary	**4·1 (1·4, 6·8)**	**4·8 (0·9, 8·7)**	**2·7 (-0·3, 5·7)**	**0·1 (-3·8, 4·1)**	**1·3 (-1·7, 4·3)**
$PM_{2·5}$		2·6 (-3·6, 8·8)	0·6 (-3·5, 4·7)	-0·4 (-4·5, 3·7)	
NO_X	3·1 (-1·3, 7·6)		-0·4 (-5·7, 5·0)	-2·1 (-6·6, 2·5)	-2·8 (-6·9, 1·4)
NO_2	4·1 (0·2, 8·1)	6·5 (-0·7, 13·8)		-1·9 (-6·7, 2·8)	-1·2 (-5·1, 2·6)
BC*	4·5 (1·8, 7·3)	7·1 (2·7, 11·4)	4·6 (1·2, 7·9)		1·0 (-2·1, 4·2)
$PM_{2·5iwa}$		7·5 (2·3, 12·7)	3·7 (0·1, 7·3)	0·9 (-3·2, 5·0)	

* Black carbon (BC) as measured by light absorption coefficient, where $0·5x10^{-5}m^{-1} \approx 0·5$ µg/m^3
Each model also included age, sex, race/ethnicity, site, scanner type, employment outside the home, smoking status, second-hand smoke exposure, physical activity, adiposity, cholesterol, statin use, neighborhood SES index, income, and education.

Table S8. Associations between predicted outdoor air pollution concentrations and CAC progression in Agatston units/year, modified by baseline participant characteristics.

Modifier	Effect of 5 µg/m^3 $PM_{2·5}$			Effect of 40 ppb NO_X		
		95% CI	P		95% CI	P
Sex			0·63			0·77
Female	3·7	(0·7, 6·8)		5·1	(0·8, 9·3)	
Male	4·5	(1·4, 7·6)		4·5	(0·2, 8·9)	
Race			0·14			0·03
White	6·6	(2·7, 10·6)		7·2	(2·0, 12·4)	
Chinese	2·2	(-1·8, 6·2)		-1·1	(-7·9, 5·7)	
African-American	6·4	(1·6, 11·2)		8·6	(3·5, 13·7)	
Hispanic	2·7	(-0·9, 6·4)		3·1	(-2·0, 8·2)	
Age at Baseline*			0·01			0·14
45-54 Years	1·4	(-1·9, 4·7)		2·6	(-2·0, 7·2)	
55-54 Years	4·0	(0·4, 7·6)		4·9	(0·1, 9·7)	
65-74 Years	8·0	(4·2, 11·7)		7·9	(3·0, 12·7)	
75+ Years	5·3	(-0·3, 11·0)		3·1	(-3·8, 10·0)	
Diabetes			0·49			0·96
Not Diabetic	4·1	(1·3, 6·9)		4·3	(0·3, 8·3)	
Impaired Fasting Glucose	5·0	(0·3, 9·6)		5·0	(-0·8, 10·8)	
Diabetes	1·6	(-3·2, 6·4)		4·3	(-1·8, 10·3)	
Hypertension			0·08			0·33
No Hypertension at Baseline	3·0	(0·1, 5·9)		4·1	(-0·2, 8·3)	
Hypertension at Baseline	5·8	(2·4, 9·1)		5·8	(1·4, 10·2)	
Obesity†			0·009			0·07
BMI <= 30 kg/m^2	5·2	(2·4, 8·1)		5·9	(1·7, 10·0)	
BMI > 30 kg/m^2	0·9	(-2·7, 4·6)		2·5	(-2·2, 7·1)	
HDL Cholesterol‡			0·52			0·90
HDL < 40 mg/dL	3·3	(-0·5, 7·1)		5·2	(-0·1, 10·4)	
HDL >= 40 mg/dL	4·4	(1·6, 7·2)		4·8	(0·8, 8·9)	
Total Cholesterol‡			0·73			0·59
< 200 mg/dL	4·2	(1·2, 7·1)		4·9	(0·8, 9·1)	
200-240 mg/dL	4·6	(1·1, 8·1)		4·1	(-0·6, 8·9)	
> 240 mg/dL	2·4	(-2·7, 7·6)		7·5	(0·9, 14·1)	
LDL Cholesterol‡			0·37			0·29
< 100 mg/dL	2·8	(-0·8, 6·3)		3·9	(-0·8, 8·7)	
100-130 mg/dL	5·8	(2·5, 9·1)		5·8	(1·3, 10·4)	
130-160 mg/dL	3·1	(-0·8, 7·0)		2·7	(-2·4, 7·8)	
> 160 mg/dL	3·7	(-1·7, 9·1)		8·6	(1·8, 15·4)	
Smoking Status§			0·97			0·50
Never	4·3	(1·3, 7·3)		6·5	(2·2, 10·8)	
Former	4·7	(1·3, 8·0)		5·3	(0·9, 9·8)	
Current	4·5	(-0·3, 9·2)		3·5	(-2·0, 9·0)	

* Cross-sectional and longitudinal adjustments for age were all categorical
† Linear adjustments for adiposity were replaced with indicator for obesity
‡ Linear adjustments for cholesterol were replaced with categories
§ Not adjusted for pack-years or second-hand smoke

Table S9. Participant characteristics at baseline by site, for participants included in the analysis of IMT. Values provided are mean (standard deviation) for continuous variables or percent for categorical variables.

Characteristic [units]	Winston-Salem	NYC	Baltimore	St. Paul	Chicago	LA
Year 2000-2010 $PM_{2.5}$ [$\mu g/m^3$]	13·5 (0·4)	14·4 (2·0)	13·6 (0·8)	10·5 (0·7)	14·1 (1·0)	17·7 (1·4)
Number of Participants						
Baseline	553	674	389	513	660	670
Follow-Up	528	630	372	477	614	624
Follow-Up Time [years]	9·5 (0·6)	9·1 (1·7)	9·5 (0·6)	9·3 (0·7)	9·4 (0·7)	8·7 (1·9)
Outcome						
Baseline [µm]	787 (186)	746 (164)	765 (180)	756 (206)	725 (163)	759 (188)
Progression [µm/year]	13 (13)	11 (15)	12 (13)	11 (16)	14 (11)	12 (15)
Demographics						
Age	60 (9)	61 (9)	61 (9)	59 (10)	61 (9)	61 (10)
Male	261 (47%)	282 (42%)	181 (47%)	261 (51%)	311 (47%)	318 (47%)
Race/Ethnicity						
White	276 (50%)	175 (26%)	220 (57%)	305 (59%)	303 (46%)	117 (17%)
Chinese	--	--	--	--	209 (32%)	221 (33%)
Black	276 (50%)	210 (31%)	169 (43%)	--	148 (22%)	82 (12%)
Hispanic	1 (0%)	287 (43%)	--	208 (41%)	--	250 (37%)
Education						
Less Than High School	24 (4%)	137 (20%)	20 (5%)	68 (13%)	37 (6%)	181 (27%)
High School	111 (20%)	124 (18%)	71 (18%)	111 (22%)	50 (8%)	123 (18%)
Some College/Technical	170 (31%)	194 (29%)	116 (30%)	187 (36%)	152 (23%)	202 (30%)
College or Graduate	248 (45%)	219 (32%)	182 (47%)	147 (29%)	421 (64%)	164 (24%)
Smoking Status						
Never	236 (43%)	350 (52%)	168 (43%)	210 (41%)	317 (48%)	413 (62%)
Former	225 (41%)	239 (35%)	175 (45%)	214 (42%)	265 (40%)	190 (28%)
Current	92 (17%)	85 (13%)	46 (12%)	89 (17%)	78 (12%)	67 (10%)
General Health Characteristics						
BMI [kg/m^2]	29 (5)	28 (5)	30 (6)	29 (5)	26 (5)	28 (6)
Systolic Blood Pressure [mmHg]	131 (21)	122 (19)	125 (18)	120 (19)	122 (20)	125 (22)
HDL [mg/dl]	50 (15)	53 (15)	51 (15)	49 (14)	54 (16)	49 (14)
LDL [mg/dl]	116 (30)	118 (32)	117 (31)	120 (30)	118 (30)	116 (32)
Total Cholesterol [mg/dl]	190 (35)	193 (35)	192 (35)	200 (37)	195 (33)	194 (37)
Hypertension	277 (50%)	288 (43%)	169 (43%)	168 (33%)	225 (34%)	276 (41%)
Statin Use	78 (14%)	114 (17%)	89 (23%)	65 (13%)	95 (14%)	95 (14%)
Diabetes						
Normal	442 (80%)	510 (76%)	300 (77%)	399 (78%)	541 (82%)	448 (67%)
IFG	60 (11%)	85 (13%)	55 (14%)	64 (12%)	76 (12%)	125 (19%)
Diabetic	51 (9%)	79 (12%)	34 (9%)	50 (10%)	42 (6%)	97 (14%)

Table S10. Associations between air pollutant concentrations and common carotid intima-media thickness (IMT) progression from staged models. Results are presented in μm/year.

Model	$PM_{2·5}$ (5 μg/m^3)	NO_X (40 ppb)	NO_2 (10 ppb)	BC (0·5 μg/m^3)*	$PM_{2·5iwa}$ (5 μg/m^3)
1	-0·9 (-3·0, 1·2)	0·4 (-1·6, 2·5)	0·0 (-1·4, 1·3)	0·7 (-0·8, 2·2)	-0·2 (-1·9, 1·4)
2	-0·7 (-2·8, 1·4)	0·4 (-1·6, 2·4)	-0·1 (-1·4, 1·3)	0·6 (-0·9, 2·1)	-0·2 (-1·9, 1·4)
3	**-0·9 (-3·0, 1·3)**	**0·2 (-1·9, 2·4)**	**-0·2 (-1·6, 1·2)**	**0·6 (-1·0, 2·1)**	**-0·4 (-2·1, 1·3)**
4	-0·3 (-2·6, 2·0)	1·1 (-1·2, 3·4)	0·5 (-1·1, 2·1)	1·1 (-0·5, 2·8)	0·0 (-1·8, 1·8)
5	-0·8 (-2·9, 1·3)	0·1 (-2·0, 2·3)	-0·3 (-1·7, 1·2)	0·3 (-1·2, 1·9)	-0·3 (-2·1, 1·4)

* BC as measured by light absorption coefficient, where $0·5x10^{-5}m^{-1} \approx 0·5$ μg/m^3

Model 1 includes age, sex, race/ethnicity, site, and scanner type

Model 2 = Model 1 + income, employment outside the home, smoking status, second-hand smoke exposure, physical activity, adiposity, cholesterol, statin use

Model 3 (main model) = Model 2 + neighborhood SES index, income, and education

Model 4 = Model 3 + hypertension, systolic and diastolic blood pressure, anti-hypertensive medication, diabetes

Model 5 = Model 4 + family history of premature CVD, fibrinogen, c-reactive protein, creatinine

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